REMARKS

Status of the Claims

By this amendment, claims 24, 26, 29, 34 and 36 are amended and claims 38-56 are added. Accordingly, upon entry of this Amendment, claims 21-56 will be pending in the application, with claims 24-28 and 34-56 ready to be examined on the merits and claims 21-23 and 29-33 withdrawn from consideration.

Exemplary support provided in the specification for the amended and new claims is given in the following table.

Page 7, lines 30-32

CLAIMS	EXEMPLARY SUPPORT IN SPECIFICATION
26	Page 7, lines 30-32
29	Page 7, lines 30-32
38	Originally filed claims and Example 8
39	Originally filed claims and Example 8
40	Originally filed claims and Example 8
41	Originally filed claims and Example 8
42	Original claim 24 and Example 8
43	Original claim 25
44	Original claim 26
45	Original claim 27 and Example 8
46	Original claim 28
47	Original claim 29
48	Original claim 30 and Example 8
49	Original claim 31
50	Original claim 32
51	Original claim 33
52	Original claim 34 and Example 8
53	Original claim 35
54	Original claim 36 and Example 8
55	Original claim 37
56	Originally filed claims and Example 8

Because the foregoing amendments do not introduce new matter, entry thereof by the examiner is respectfully requested.

Objections to the Specification

The examiner states that page 8, line 19 should say "clone", not "close". Additionally, the examiner states that page 9, line 37 should say "marker", not "market". Applicants have amended the specification as suggested by the examiner. Therefore, applicants respectfully request reconsideration and withdrawal of the objection.

Objections to the Drawings

The examiner asserts that the brief description of the figures for Figures 6 and 7 appear to be switched. The examiner also states that the description of Figure 9 refers to parts A-E, however, the Figure only shows parts A and B. Finally, the examiner states that Figure 10 has handwriting which labels these Figures as "fig 1A-F" though it is figure 10 and that the Brief Description of the Figures should also refer to Figures 10 A-F. Attached herewith, Applicants submit formal drawings. These formal drawings were submitted in U.S. Application No. 08/461,436 (U.S. Patent No. 6,146,852), of which U.S. Application No. 08/340,664 is a divisional application. The present application is a continuation of U.S. Application NO. 08/340,664. Applicants have amended the "Brief Description of the Drawings" section to correspond to the formal drawings. Therefore, applicants respectfully request reconsideration and withdrawal of the objection.

Claim Objections

Claims 27, 34 and 36 are objected to by the examiner under 37 C.F.R. § 1.75 as being substantial duplicates of claim 24. Claim 28 is objected to by the examiner under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 25. Claim 29 is objected to by the examiner under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 26. Applicants respectfully request reconsideration and withdrawal of the objection.

The examiner asserts that claims 27-29, 34 and 36 all recite various methods to obtain recombinant hPTH; however the claims are drawn to recombinant hPTH and are, therefore, substantial duplicates of claims 24-26. Applicants do not agree. Applicants assert that claims 24-26 are different from claims 27-29, 34 and 36 because the terms used to define the leader

expressed with hPTH are different. For example, in claim 24, the leader sequence corresponds to the DNA sequence encoding *Saccharomyces* mating factor α1 lacking the yeast STE13 recognition. In contrast, in claim 27, the leader sequence comprises the first nineteen amino acids of the DNA sequence encoding *Saccharomyces* mating factor α1. Additionally, the leader sequence in claims 34 and 36 is defined differently than the leader sequence in claim 24 and 27. Therefore, claims 27, 34 and 36 are not substantial duplicates of claim 24, claim 28 is not a substantial duplicate of claim 25 and claim 29 is not a substantial duplicate of claim 26.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 34 and 35 are rejected by the examiner under 35 U.S.C. 112, first paragraph, for allegedly lacking written description. The examiner asserts that applicants have not provided a written description of an "optimized" consensus signal sequence. Applicants respectfully traverse and request reconsideration and withdrawal of the rejection.

Applicants direct the examiner's attention to page 24, line 7 through page 26, line 8 of the present specification where optimized consensus signal sequences are described. The specification defines an "optimized consensus signal sequence" as any amino-terminal amino acid sequences composed of (1) an amino-terminal positively charged region, (2) a hydrophobic core region, and (3) a polar COOH-terminal region composed of five amino acids (from position -5 to -1 relative to the cleavage site) that defines the cleavage site.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 24-29 and 34-37 are rejected by the examiner under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. Applicants respectfully request reconsideration and withdrawal of the rejection.

A. The examiner asserts that in claim 24, the recitation of "STE 13 recognition" in part (a)(1) is allegedly indefinite. Applicants have amended claim 24 to recite "STE 13 recognition site". Therefore, claim 24, as amended, complies with the requirements of 35 U.S.C. § 112, second paragraph.

B. The examiner asserts that in claims 24-29 and 34-37 the phrase "composition comprising" is allegedly indefinite because a composition comprises two or more substances, yet according to the Examiner, the claims recite only one substance (hPTH). Applicants note that the term "comprising" is an open ended recitation. Therefore, the phrase "a composition comprising", as used in the present claims, is not indefinite.

C. The examiner asserts that in claims 24-29 and 34-37 it is allegedly unclear if and where the leader sequence is cleaved. Applicants assert that the present specification clearly describes when and where the leader sequence is cleaved. In order to clarify the cleavage of the leader sequence, applicants offer the following description.

A feature of the present invention is the use of cleavable leader sequences that protect the N-terminus of the expressed product, to permit the PTH to remain intact for isolation/purification. Applicants direct the examiner's attention page 6, lines 25-28, of the specification where it states that "[d]uring the secretion process, the α-factor leader sequence is cleaved off by an endopeptidase specific for a dibasic amino acid sequence and encoded by the KEX2 gene." Biologically, the host expresses a gene in which DNA coding for hPTH is coupled with DNA coding for a leader sequence. When expressed, the gene yields a protein in which the leader is fused to the N-terminus of PTH. However, the product that is recovered from the host is "clean" hPTH(1-84), which is the authentic form of the native human PTH (the leader sequence has been cleaved). As shown in the examples of the present application, the leader is cleaved from the leader-PTH product by the very yeast cells that produce it. The examples illustrate that while the yeast produces PTH initially as a leader-PTH fusion, the product can be recovered in final form as authentic PTH ("clean" hPTH(1-84)) because the yeast has cleaved the leader from the expressed leader-PTH product.

D. The examiner asserts that in claims 26 and 29, it is allegedly unclear whether the protein has been purified to greater than 90% before it was part of the claimed composition, or if the purified protein comprises greater than 90% of the composition. Applicants have amended claims 26 and 29 to recite that the hPTH(1-84) protein of step (c)

has a purity of greater than 90%. Therefore, claims 26 and 29, as amended, comply with the requirements of 35 U.S.C. § 112, second paragraph.

E. The examiner asserts that in claim 29 the recitation "the protein" lacks antecedent basis. Applicants have amended claim 29 to comply with the requirements of 35 U.S.C. § 112, second paragraph.

F. The examiner asserts that in claim 34, the phrase "optimized consensus signal sequence" is unclear. As discussed above in response to the examiner's rejection of claims 34 and 35 under 35 U.S.C. § 112, first paragraph, on page 24, line 7 through page 26, line 8 of the present specification, optimized consensus signal sequences are described.

The examiner further asserts that in claim 34 it is not understood how a DNA sequence can have the properties listed in parts (2)(I) - (2)(iii) of the claims since these claim properties of proteins. Applicants have amended claim 34 to clarify the DNA and protein components within the microorganism. Therefore, claim 34, as amended, complies with the requirements of 35 U.S.C. § 112, second paragraph.

G. The examiner asserts that in claim 35 the term "optimized" is allegedly unclear. As discussed above in response to the examiner's rejection of claims 34 and 35 under 35 U.S.C. § 112, first paragraph, on page 24, line 7 through page 26, line 8 of the present specification, optimized consensus signal sequences are described.

H. The examiner assert that in claim 36 there is allegedly insufficient antecedent basis for "the expression product". Applicants have amended claim 36 by deleting the term "expression product". Therefore, claim 36 complies with the requirements of 35 U.S.C. § 112, second paragraph.

I. The examiner asserts that in claim 36, the phrase "expression product" is unclear. Applicants have amended claim 36 by deleting the term "expression product". Therefore, claim 36 complies with the requirements of 35 U.S.C. § 112, second paragraph.

Claim Rejections - 35 U.S.C. § 101 (Statutory Double Patenting)

Claims 24-26 were rejected as allegedly claiming the same invention as that of claim 3 of U.S. Patent No. 5,420,242 ("the '242 patent"). Applicants respectfully request reconsideration and withdrawal of the rejection

Applicants assert that claims 24-26 of the present application are distinct from claim 3 of the '242 patent. Claim 3 of the '242 patent recites "[a]n intact human parathyroid hormone operably linked to a modified *Saccharomyces* mating factor alpha 1..." In contrast, Claim 24 of the present application recites "[a] composition comprising recombinant human parathyroid hormone (hPTH) (1-84) wherein the hPTH is made by a process comprising the steps of..."

A feature that is present in the product of claim 3 of the '242 patent yet not present in the product formed by the process of claim 24 of the present application is that the PTH is operably linked to the leader. In other words, the product of claim 3 of the '242 patent is a leader-PTH product, whereas the product of claim 24 of the present invention is "clean" hPTH(1-84). In the process of claim 24, the host expresses a gene in which DNA coding for hPTH is coupled with DNA coding for a leader sequence. When expressed, the gene yields a protein in which the leader is fused to the N-terminus of PTH. However, the product that is recovered from the host is "clean" hPTH(1-84), which is the authentic form of the native human PTH (the leader sequence has been cleaved). As shown in the examples of the present application, the leader is cleaved from the leader-PTH product by the very yeast cells that produce it. The examples illustrate that while the yeast produces PTH initially as a leader-PTH fusion, the product can be recovered in final form as authentic PTH ("clean" hPTH(1-84)) because the yeast has cleaved the leader from the expressed leader-PTH product.

Claim Rejections - 35 U.S.C. § 101 (Obviousness-type Double Patenting)

Claims 24-26 are rejected by the examiner under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 3 of the '242 patent. As discussed above, the product of claim 3 of the '242 patent is distinct from the product formed by the process of claim 24 of the present application. The product of claim 3

is a leader-hPTH product, whereas the product of claim 24 is "clean" hPTH(1-84). Since the product of claim 24 of the present application is not rendered obvious by claim 3 of the '242 patent, applicants respectfully request reconsideration and withdrawal of the rejection.

Claim Rejections - 35 U.S.C. § 102

Claims 24-29 and 34-37 are rejected by the examiner under 35 U.S.C. § 102 as being allegedly anticipated by Keutmann et al. and Kimura et al. The Examiner asserts that the present application claims recombinant PTH made by various methods, but that the claims are drawn to *compositions* comprising the hPTH. The Examiner asserts that purified hPTH would be the same molecule regardless of how the hPTH is made. The Examiner further asserts that Keutmann et al. and Kimura et al. teach compositions of purified human PTH (1-84) (*see* page 5723, last two paragraphs of the Introduction; first paragraph of "Materials and Methods"; and Figure 7 of Keutmann et al.; and Abstract of Kimura et al.). Therefore, the Examiner concludes that Keutmann et al. and Kimura et al. meet the limitations of claims 24-29 and 34-37. Applicants respectfully traverse and request reconsideration and withdrawal of the rejection.

The hPTH of the present invention is distinct from the hPTH of the cited art because the hPTH of the present invention is recombinant while the hPTH of Keutmann et al. and Kimura et al. is purified from a human source. Applicants do not agree with the examiner's assertion that the hPTH of the present invention and the cited are is the same molecule regardless of how the hPTH is made. This is because the recombinant hPTH of the present invention is produced by a microorganism, signifying that the hPTH of the present invention cannot contain any contaminating proteins of human origin. In contrast, it is likely that the hPTH of Keutmann et al. and Kimura et al. teach compositions contaminated by proteins of human origin, since the source of the hPTH in these references is human. Therefore, the distinction of the present invention in view of the cited art is that the hPTH of the present invention is recombinant. This distinction is bolstered by the fact that the hPTH of the present invention is produced by a microorganism. Thus, the present invention is not anticipated by Keutmann et al. and Kimura et al.

Newly Added Claims 38-56

Newly added claims 38-56 are free of the cited art. At the time of the priority date of the present application, it was not possible to produce a useful microbial source of PTH. The human PTH produced by prior art microbes at the priority date of the present application was of poor, degraded quality. The present inventors discovered that if the N-terminus of the PTH is protected, by enabling the microbe to produce PTH in a form having the N-terminus coupled to a leader that can be removed by the microbe itself or by humans following isolation, a useful microbial source of intact PTH would be possible. As shown in the examples of the present specification, the PTH product obtained is substantially devoid of PTH fragments, which are the most common undesired product of prior art recombinant systems for PTH production. The newly added claims are distinct from the prior art recombinant systems because the claims require that the extract from which the PTH is ultimately obtained is itself relatively pure with respect to its PTH component (i.e., the PTH component within the extract does not comprise any significant amount of digested PTH because it has all been protected from degradation by the N-terminal leader sequence which is removed by the cells before the PTH is recovered). Therefore, applicants respectfully request allowance of newly added claims 38-56.

CONCLUSION

As the above-presented amendments and remarks address and overcome all of the rejections presented by the examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

If the examiner has any questions concerning this application, he or she is requested to contact the undersigned.

Respectfully submitted,

Date November 29, 2001

By _____

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicant
Registration No. 34,717

Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

On page 8, the fifth full paragraph:

Figure 5 shows the actual amino acids sequence of the human preproparathyroid hormone for which the DNA sequence in [close] clone pSShPTH-10 codes.

On page 8, the sixth full paragraph:

Figure 6 shows the sequence (SEQ ID NO: 7) of the MFα1-hPTH fusion gene [with all possible combinations of the DNA coding for hPTH].

On page 8, the seventh full paragraph:

Figure 7 shows the sequence (SEQ ID NO: 8) of the MFα1-hPTH fusion gene with all possible combinations of the DNA coding for hPTH.

On page 9, the first full paragraph:

Figures 9A-B show the purification of recombinant hPTH [from the growth] medium including: FIG. 9A, a chromatogram of the HPLC purification; in FIG. 9B a chromatogram of the HPLC purification of fractions 32 and 33 from panel 9A (the peak of the recombinant hPTH is indicated in black); an HPLC of one microgram standards hPTH (1-84); and a co-chromatogram of the recombinant PTH from the first chromatogram and one microgram standard of hPTH.

[A: Chromatogram of the 1.HPLC purification

B: Chromatogram of the 2.HPLC purification of fractions 32 and 33 from panel A. The peak of the recombinant hPTH is indicated by black.

C: 2.HPLC run of 1 ug standard hPTH (1-84)

D: Co-chromatography of the recombinant PTH pack from panel B and 1 ug of standard hPTH (1-84)

E: Silver staining of SDS-PAGE of the proteins in the hPTH pack

1: recombinant hPTH, 1 ug

2: hPTH (1-84) (σ), 3ug (Note HMW Impurities)

On page 9, the second full paragraph:

Figures 10A-G [10] show construction of PPTH-M13-ΔEA/KQ.

On page 9 and bridging page 10, the last full paragraph:

Figure 13. Purity of purified hPTH (1-84,Q26). Yeast growth medium fromyeast strain BJ1991 transformed with the expression plasmids pαUXPTH-Q26 were concentrated and purified by reversed phase HPLC as described in Experimental Protocol. The purity of the recombinant hormone was then analyzed by analytical HPLC (Panel A) and SDS PAGE (Panel B, lane 2). In Panel B the purified hPTH (1-84,Q36) is compared with the wild type hormone purified by two runs on HPLC (lane 3). The molecular weight [market] marker in lane M is the same as in Figure 2. Lane 1 shows a reference PTH produced in *E. coli*.

IN THE CLAIMS:

24. (Amended) A composition comprising recombinant human parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

(a) providing a microorganism comprising:

(1) a leader sequence corresponding to the DNA sequence encoding *Saccharomyces* mating factor α1 lacking the yeast STE13 recognition site; and

(2) a DNA sequence encoding hPTH, wherein the leader sequence and the hPTH sequence are operably linked;

(b) culturing said microorganism to allow expression of said DNA sequence encoding hPTH, thereby producing hPTH (1-84); and

(c) purifying the resultant hPTH (1-84) protein.

26. The composition of claim 24, wherein the hPTH protein of step (c) has a purity of greater than 90%.

29. The composition of claim 27, wherein [the protein] said hPTH (1-84) protein of step (c) has a purity of greater than 90%.

34. (Amended) A composition comprising recombinant parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

(a) providing a microorganism comprising a DNA sequence which encodes:

(1) an optimized consensus signal sequence having the following:

[(1) a leader sequence; and

(2) a DNA sequence encoding hPTH comprising an optimized consensus signal sequence having the following:]

(i) a positively charged amino-terminal;

(ii) a hydrophobic core region; and

(iii) a polar COOH-terminal region[,];

(2) a leader sequence, and

(3) a DNA sequence encoding hPTH, wherein the signal sequence, the leader sequence and the sequence encoding hPTH [sequence] are operably linked;

(b) culturing said microorganism to allow expression of said DNA sequence encoding hPTH, thereby producing hPTH (1-84); and

(c) purifying the resultant hPTH (1-84) protein.

36. (Amended) A composition comprising recombinant parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

(a) providing a microorganism comprising a DNA sequence which encodes:

(1) a leader sequence; and

(2) a DNA sequence encoding hPTH comprising a functional signal sequence encoded by an amino-terminal amino acid sequence, [the expression product of which can direct] wherein said amino-terminal amino acid sequence is capable of directing secretion in yeast, and wherein the leader sequence and the sequence encoding hPTH [sequence] are operably linked;

(b) culturing said microorganism to allow expression of said DNA sequence encoding hPTH, thereby producing hPTH (1-84); and

(c) purifying the resultant hPTH (1-84) protein.